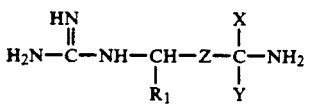
METHOD OF INHIBITING PROTOZOAL GROWTH

This is a continuation of application Ser. No. 07/453,011, filed Dec. 20, 1989, now abandoned, which is a continuation of Ser. No. 07/330,967, filed Mar. 28, 1989, now abandoned, which is a continuation of application Ser. No. 205,039, filed Jun. 7, 1988, now abandoned, which is a continuation of application Ser. No. 930,055, filed Sep. 2, 1987, abandoned, which is a continuation of application Ser. No. 931,591, filed Nov. 25, 1986, abandoned, which is a continuation in part of application Ser. No. 811,147, filed Dec. 19, 1985, abandoned.

This invention relates to the use of certain irreversible enzyme inhibitors which interrupt the biosynthesis of polyamines and which inhibit the growth of certain protozoans.

More specifically this invention relates to certain agmatine and arginine derivatives which are enzyme inhibitors useful in the treatment of animals suffering from disease states caused by parasitic infections with certain protozoa.

Still more specifically, this invention relates to X-substituted arginine and agmatine compounds having the formula



I

their pharmaceutically acceptable salts, their individual optical isomers and mixtures thereof, wherein R_1 is H or CH_3, Z is $-CH_2-CH_2-$ or $-CH=CH-$, X is $-CH_2F$, $-CHF_2$, $-CHCl_2$, $-CHClF$, $-C\equiv CH$ or $-CH=C=CH_2$, Y is H or COOR with R being H or C_{1-18} alkyl, which compounds are enzyme inhibitors useful in the treatment of certain disease states in animals, including man, said disease states being caused by infection of the animals with certain protozoa. In those instances wherein Z is —CH=CH—, the double bond preferably is in its trans configuration, i.e. the (E) designated compound.

In essence the compounds depicted by formula I are halomethyl, acetylenic, or allenic derivatives of arginine and agmatine or their dehydro derivatives. For the most part these compounds are known and their preparation is adequately described in the prior art. In those specific instances wherein the compounds are novel, per se, such compounds may be prepared by methods and techniques analogously known in the art. For example, the halomethyl derivatives of the amines (i.e. Y is H and Z is $-CH_2-CH_2-$) may be prepared by the techniques of U.S. Pat. No. 4134918, and the dehydro analogs thereof by using the techniques of British Patent No. 2083030 and with the techniques hereinbelow illustrated by Examples 1-3. The halomethyl derivatives of the α-amino acids (i.e. Y is COOR) may be prepared by the teachings of South African Patent No. 78/3349 and their dehydro derivatives may be prepared by the teachings of British Patent No. 2083030. The acetylenic derivatives of the amino acids (i.e. Y is COOR and X is —C≡CH) may be prepared by the teachings of U.S. Pat. No. 4182891 and of the amines (i.e. Y is H and X is C≡CH) may be prepared by the teachings of 4139563. The allenic derivatives of the compounds of formula I may be prepared from the acetylenic derivatives by the techniques of U.S. Pat. No. 4,454,156 which are further elaborated upon by Casara in Tetrahedron Letters, Vol. 25, pg. 1891 (1984).

The technique for selectively converting an amino moiety to a guanidino moiety is illustrated by the following specific examples. This technique is generally available to make compounds of formula I from intermediates which are analogous to those used in these examples.

EXAMPLE 1

1-Guanidino-4-amino-5-hexyne dihydrochloride

Triethylamine (4.5 ml, 30 mmoles) is added to a solution of 1,4-diamine-5-hexyne dihydrochloride (1.85 g, 10 mmoles) in water (50 ml) at −10° C. To this solution 3,5-dimethylpyrazole-1-carboxamidine nitrate (2.3 g, 10.5 mmoles) is slowly added (in small portions) and the resulting mixture is stirred 2 h at −10° C., and for 3 days at room temperature after all starting materials have reacted (this is controlled by electrophoresis and ninhydrin colorimetric analysis). Then, the mixture is acidified (pH 5-6) with a 1 M solution of HCl and washed with dichloromethane (2×100 ml). The aqueous layer is concentrated under reduced pressure to a volume of 5 ml. This concentrated mixture is purified by ion exchange chromatography. (DOWEX 50W-X8, 100-200 mesch, H+Form) which is eluted by using a gradient of solution of HCl (0 to 4 N). The eluted fractions are checked by electrophoresis on silica gel plates and colorimetric analysis (ninhydrin and Sakaguchi reagent). The fractions containing the guanidino material are concentrated together under reduced pressure to give the title compound (1.7 g) as a colorless oil. NMR(^{1}H) δ ppm. 1.76 (m, 4H); 2.96 (d,1H,J=1H_2); 3.16 (m, 2H) 4.2 (m, 1H). M/Z: MH+ 155; MH± NH_3: 138; MH± NH_2—$CNHNH_2$=98.

EXAMPLE 2

1-Fluoro-2-amino-5-guanidinopentane dihydrochloride

Using the procedure similar to that described in the first example 1-fluoro-2,5-diaminopentane dihydrochloride (1.93 g, 10 mmoles) afforded 1.9 g of the title compound, mp: 158° C. after recrystallization from ethanol/ether.

Similarly, using the procedure similar to that described in the first example, 4,7-diamino-1,2-heptadiaene dihydrochloride (2.0 g, 10 mmole) afforded 2.1 g of 4-amino-7-guanidino-1,2-heptadiene dihydrochloride as an oil.

EXAMPLE 3

(E)α-Fluoromethyl-3,4-dehydro arginine monohydrochloride

Using the procedure similar to that described in example one (E)- -fluoromethyl-3,4-dehydro ornithine monohydrochloride (1.8 g, 10 mmole) in 50 ml of water, triethylamine (3 ml, 20 mmoles) and 3,5-dimethylpyrazole-1-carboxamidine nitrate (2.5 g, 1.1 mmoles) yielded, after two weeks at room temperature, 2.2 g of the title compound as a white solid, which was recrystallized from absolute EtOH (mp 171° C., decomp.). H_1NMR Data: (D_2O, DCl) (^{1}H) δ (ppm) 4.0 (d, 2H) 4.65 (q, 1H), 5.25 (q, 1H) 5.75 (m, 2H)

Using the procedure similar to that described in example three, α-fluoromethyl ornithine monohydrochloride (2.0 g, 10 mmoles) afforded 2.05 g of α-